UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

007846

APR - 2 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: EPA ID # 7969-53. DER for an Interim Report of a Dermal Developmental Toxicity Study of Vinclozolin in the rat/34R0375/88074 (MRID No. 413250-00 and 413250-01).

Tox. Chem. No.: 323C.
Project No.: 0-0512.
Record No.: 257840.

To: S Lewis/J Stone, PM 21
Registration Division (H7505C)

From: David G Anderson, PhD. David G Anderson 3/14/90
Section 2, Toxicology Branch I (IRS)
Health Effects Division (H7509C)

Thru: Marion Copley, DVM
Section Head, Section 2
Toxicology Branch I (IRS)
Health Effects Division (H7509C).

CONCLUSIONS:

These conclusions are tentative because the submitted interim report lacked sufficient detail to verify the results.

This is a preliminary report on a dermal developmental toxicity study. The full report is scheduled to be submitted in April 1990.
Doses Administered: 0, 60, 180, and 360 mg/kg/day, applied dermally to 25 Wistar rats/group.

Developmental Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, and hydroureter in fetuses, but not in litters occurred at 180 mg/kg/day and higher.

Maternal Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for increases in absolute adrenal weights and at 360 mg/kg/day increases in absolute liver weights.

Core classification: Supplementary because it is a preliminary study which results in insufficient experimental detail for complete evaluation. Full study will be submitted in April 1990.

Requested Action:
The registration Division requested that the Toxicology Branch 1 (IRS) review preliminary data on a dermal developmental toxicity study with Vinclozolin.

C. COMMENTS:
In this dermal study, the effect level for decreased anal-genital distance in males is 180 mg/kg/day and the NOEL is 60 mg/kg/day. The effect level for these same effects is 50 mg/kg/day and the NOEL is 15 mg/kg/day in an oral gavage study. Preliminary results from a percutaneous penetration study indicates that 26% of the dose applied is absorbed. Thus, a dermal dose with a NOEL of 60 mg/kg/day is calculated to be equivalent to an oral dose of 15.6 mg/kg/day [(60 mg/kg/day) X (0.26) = 15.6 mg/kg/day], and a corresponding dermal LEL of 180 mg/kg/day is calculated to be equivalent to an oral dose of 46.8 mg/kg/day [(180 mg/kg/day) X (0.26) = 46.8 mg/kg/day]. These results indicate that the dose levels from the oral developmental toxicity studies are supported by the dose levels from the dermal developmental toxicity study. In addition, the NOEL and LEL for adrenal weight increase in this dermal developmental toxicity study is identical with the NOEL and LEL for the pseudohermaphrodism, respectively.

Cover memo on a preliminary data on dermal developmental toxicity/Rat/B:\VINCLV13.23C\ MDERMDEV.PRE/D Anderson/3/13 90.

2

Primary reviewer: David G Anderson, PhD. David M Anderson 3/14/90
Section VII, Tox. Branch (H7509C).
Secondary reviewer: Marion Copley, DVM. Marion Copley 3/29/90
Section VII, Tox. Branch (H7509C).

PRELIMINARY DATA EVALUATION REPORT

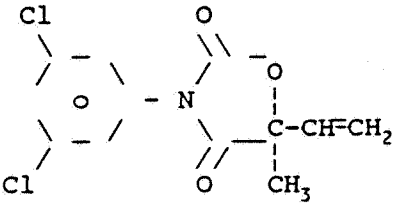
STUDY TYPE: Preliminary Dermal Developmental Toxicity Study/83-3/Rat/34R0375/88074.

TOX. CHEM. No.: 323C

MRID No.: Summary-413250-00.
Data and tables-413250-01.

TEST MATERIAL: Vinclozolin, technical; A.I. is [3-(3,5-dichlorophenyl)-5-ethenyl-5-methyl-2,4-oxazolidinedi-2,4-one].

STRUCTURE:



SYNONYMS: Ronilan 50W, 50% A.I., Ronilan FL, 41% A.I.

SPONSOR: BASF Corp. Chemicals Div., Ag. Chem., 100 Cherry Hill Road, Parsippany, NJ 07054.

TESTING FACILITY: BASF Aktiengesellshaft, Dept. Toxicology, 6700 Ludwigshafen, Federal Republic of Germany.

STUDY NO.: 34R0375/88074.

REPORT TITLE: Prenatal Toxicity Studies in Rats (Dermal application).

AUTHOR(S): Not specified.

REPORT ISSUED: December 7, 1989.

CONCLUSIONS: This is preliminary report on a dermal developmental toxicity study.
Doses Administered: 0, 60, 180, and 360 mg/kg/day, applied dermally to 25 Wistar rats/group.

3

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 34R0375/88074.

Developmental Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for decreased anal-genital distance in males (pseudohermaphroditism). Increased incidence of dilated renal pelvis, and hydroureter in fetuses, but not in litters occurred at 180 mg/kg/day and higher.

Maternal Toxicity:
NOEL: 60 mg/kg/day.
LEL: 180 mg/kg/day for increases in absolute adrenal weights and at 360 mg/kg/day increases in absolute liver weights.

Core classification: Supplementary because it is a preliminary study which results in insufficient experimental detail for complete evaluation. Full study will be submitted in April 1990.

A. MATERIALS:

1. Test compound:Vinclozolin, Description: Not specified. Purity: Not specified.

2. Test animals: Species: Rats, Strain: Wistar.

3. Environmental: Not specified.

B. STUDY DESIGN: This study is a dermal developmental toxicity study conducted in rats. Vinclozolin was applied to the clipped backs of 25 female rats/group at 0, 60, 180 and 300 mg/kg/day from gestational day (gd) 6 through 19 for 6 hours/day[1]. A standard dose volume of 5 ml/kg was used. The vehicle was distilled water and 0.5% carboxymethylcellulose. The method of protecting the application site was not stated. Clinical observationswere conducted daily. The application site was inspected twice daily at the time of application and after 6 hours. Food consumption and body weight gain were determined regularly. At gd 20 in dams, blood was drawn and the animals were sacrificed. Gross necropsy was conducted on the dams, and livers, adrenals and carcasses were weighed. Fetuses were weighed, the soft tissue and skeletons examined, and anal-genital distance determined relative to body weight.

[1] The dosing from gd 6 to 19 is a deviation from Guideline 83-3 which recommends dosing from gd 6 to 15. However, the effect on the anal-genital distance can not be demonstrated where dosing is terminated at day 15.

4

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 84R0375/88074.

Test Group	Dose mg/kg/ day	Volume of Doses ml/kg/day	Conc. in mg/100 ml	Number of Females
1. Cont.	0.5% CMC in water vehicle	5	-	25
2. Low (LDT)	60	5	-	25
3. Mid (MDT)	180	5	-	25
4. High(HDT)	300	5	-	25

History - This was conducted in response to a study in Japan under Japanese guidelines for BASF Japan (K Takehara, M Itabashi, T Inoue and M Tajima, "Teratogenicity Study of Vinclozolin (BAS-352F) to Rats in Dietary Administration", conducted by Nippon Institute for Biological Science, 2221-1 Shin-machi, Ohme-shi, Tokyo 198, December 1979 for BASF Japan. This study from Japan differed from EPA guideline studies essentially in that the test material was administered in the diet, and from gd 0 through 21, 11 days longer than OPP requirements of gd 6 through 15. This study was also conducted for a longer dosing period, 6 through 19, but the dose was applied dermally. The full report is scheduled to be submitted in April 1990. **This preliminary study demonstrated effects on the anal-genital distance in males, and verifies the study results from Japan.**

C. METHODS AND RESULTS:

1. Clinical Signs - No clinical signs occurred at any dose level.

2. Body Weight - They were weighed on gd 0, 1, 3, 6, 8, 10, 13, 15, 17, 19, and 20. The body weight gain was determined between successive weighings.

Results - Body weights and body weight gain did not appear to demonstrate a significant dose related decrement or elevation. However, statistically significant increases in body weight gain were noted at the 360 mg/kg/day between gd 13 and 15 only. Body weight gain was nominally elevated in the 360 mg/kg/day dose group during other gestational days. The carcass weight and the gravid uterine weight was also nominally elevated in the 360 mg/kg/day dose group. Although there was a slight trend to increasing body weight, the effect was minimal and not significant.

5

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 34R0375/88074.

3. Food consumption - Food consumption was determined and mean daily intake was calculated. Efficiency was not specified.

Food consumption was determined gd 0 to 1, 1 to 3, 3 to 6, 6 to 8, 8 to 10, 10 to 13, 13 to 15, 15 to 17, 17 to 19, and 19 to 20.

Results - Food consumption was nominally elevated in the 360 mg/kg/day dose group. Non of the values were significantly different from control values. The relative efficiency of food utilization from gd 6-19 was 3.63 in controls, 3.73 at 60 mg/kg/day, 3.70 at 180 mg/kg/day and 3.83 at 360 mg/kg/day. Although a trend of increasing efficiency is noted, with variability of the data this trend may be incidental. However, the trend is consistent with a trend for increasing body weight gain with increasing dose level.

4. Blood was collected - Blood was collected from the retroorbital venus plexus. Blood was collected on gd 20. When a percent change is reported in parentheses, it refers to percent of control values.

The CHECKED (X) parameters were examined.

a. Hematology -

X Hematocrit (HCT)*	Total plasma protein (TP)
X Hemoglobin (HGB)*	Leukocyte differential count
X Leukocyte count (WBC)*	X Mean corpuscular HGB (MCH)
X Erythrocyte count (RBC)*	X Mean corpuscular HGB conc.(MCHC)
X Platelet count*	X Mean corpuscular volume (MCV)
X Reticulocytes (RETI)	

Results - Platelets (93%) and MCHC (97%) were statistically significantly depressed at 360 mg/kg/day. Reticulocytes were nominally elevated at all dose levels. The effects on the platelets, MCHC and reticulocytes were minimal and may not have been test material related.

5. Necropsy of Mothers and Fetal Examinations: Dams were sacrificed on gd 20. Pregnant uteruses were weighed and subtracted from the weight of the dam. The corpora lutea, the number of viable fetuses, dead fetuses, resorptions, and implantation sites were counted. Fetal weights were determined and malformations and variations were determined. The ratio of the anal-genital distance to body weight was determined.

a. Gross pathology on Mothers - No dose related gross pathological effects were reported.

6

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 34R0375/88074.

b. Results on Mothers - The carcass weight of dams, and the gravid uterus was not statistically significantly different from control values. Absolute liver weights (107% of control values) were statistically significantly increased at 360 mg/kg/day and absolute adrenal weights (109-111% of control values) were statistically significantly increased at 180 and 360 mg/kg/day. The relative weights of these organs were only nominally elevated in the two highest dose groups.

Reproduction data and corpora luteal counts, implantation loss, and post-implantation loss did not differ from control values. However, pre-implantation loss was nominally reduced in the highest dose group and post-implantation loss was nominally decreased in all dose groups.

c. Results of the Fetal Examination - The fetal anal-genital distances are reported in Table 1-018. A statistically significant dose related decrease in the ratio of the anal-genital distance to the body weight occurred in male fetuses at 180 mg/kg/day and higher. (In other studies, MRID # 411322-01, the male fetuses in the 1000 mg/kg/day dose group looked like females, but on examination of the placement and appearance of the male gonads, they appeared to be superficially normal. On this basis the phenomenon was considered to be pseudohermaphroditism.)

Fetal weights did not differ from control values. Early, resorptions did not differ from control values. However, late resorptions were statistically significantly reduced in the 360 mg/kg/day dose group. The number of live fetuses were nominally elevated in all dose groups.

On soft tissue examination, the combined incidence of dilated renal pelvis and hydroureter in fetuses but not in litters were each statistically significantly elevated at 360 mg/kg/day. The incidence in litters was nominally elevated at 360 mg/kg/day.

On skeletal examination, the combined incidence of fetuses with total variations and retardations was statistically significantly increased, but not for litters at 60 and 180 mg/kg/day. Reduced ossification of the sternebrae at the 180 mg/kg/day dose level were statistically significant in litters. In other studies (MRID # 41132-01) the incidence of 14th rib may have been elevated but this effect did not occur in this study. The statistically significant effects occurring at 60 and 180 mg/kg/day may not have been dose related since they did not exhibit a good dose relationship and they were not significant at 360 mg/kg/day.

7

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 34R0375/88074.

D. DISCUSSION AND ABSTRACT:

Vinclozolin was administered dermally (vehicle water and 0.5% carboxymethylcellulose) to 25 rats/group at 0, 60, 180, and 360 mg/kg/day from gestational day (gd) 6 through 19. At gd 20 the fetuses were stated to be investigated by methods outlined in OECD and FIFRA guidelines. Marginal maternal toxicity was demonstrated by the statistically significant increase in absolute adrenal weight at 180 and 360 mg/kg/day. No dose related gross abnormalities were noted in the kidneys. No histology was conducted on the organs. A statistically significant increase occurred during gd 13-15 in the body weight gain. The carcass weight and the body weight gain were all nominally elevated at 360 mg/kg/day over control values at gd 20. The body weight gain may have been test material related, but the effect was not statistically significant.

Male and female fetal body weights were not statistically significantly different from control values.

Pre-implantation losses were nominally decreased and the number of live fetuses were nominally increased which are consistent with the statistically significant decrease in late resorptions at the 360 mg/kg/day dose level.

A statistically significant increase occurred in pseudohermaphroditism among male fetuses. The term pseudohermaphroditism was used to describe the effect because these males exhibited decreased anal-genital distances, but exhibited superficially normal internal testes. The anal-genital distance/body weight ratio in male fetuses was statistically significantly decreased at 180 mg/kg/day and higher. The response was dose related. These results are consistent with possible anti-hormonal effects from the test material.

Soft tissue examination of fetuses indicated a statistically significant increased incidence in dilated renal pelvis and a nominal increase in hydroureter, but the effect was only nominally elevated in litters at 360 mg/kg/day.

Skeletal examination of fetuses indicated increased incidence of variations and retardations (reduced sternebrae ossification) at 60 and 180 mg/kg/day but not at 360 mg/kg/day. There were no indications of an increased incidence of 14th rib in these studies as there had been in other oral studies (MRID = 411322-01) in the rat.

In summary, marginal effects occurred for increased soft tissue variations at 360 mg/kg/day(HDT) and statistically significant decreases occurred in the anal-genital distance in males at 180 mg/kg/day and above. The NOEL is 60 mg/kg/day. In the oral study the effect level for these same effects is 50 mg/kg/day and the NOEL is 15 mg/kg/day. Preliminary results from a percutaneous penetration study indicates that 26% of the dose applied is absorbed. Thus, a dermal dose with a NOEL of 60 mg/kg/day is calculated to be equivalent to an oral dose of 15.6

8

Preliminary Dermal Developmental Toxicity Study/83-3/ Rat/ 34R0375/88074.

mg/kg/day [(60 mg/kg/day) X (0.26) = 15.6 mg/kg/day], and a corresponding dermal LEL of 180 mg/kg/day is calculated to be equivalent to an oral dose of 46.8 mg/kg/day [(180 mg/kg/day) X (0.26) = 46.8 mg/kg/day]. These results indicate that the dose levels from the oral developmental toxicity studies are supported by the preliminary data from the percutaneous absorption study and the dose levels from the dermal developmental toxicity study. In addition, the NOEL and LEL for adrenal weight increase in this dermal developmental toxicity study is identical with the NOEL and LEL for the psuedohermaphrodism, respectively.

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9